Individualized treatment approaches for Langerhans cell histiocytosis

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Abstract: Langerhans cell histiocytosis (LCH) belongs to the rare histiocytic disorders, and has an estimated incidence of 1-2 cases per million adults [1]. Myeloid dendritic cells that express the same antigens (CD1a, CD207) as epidermal Langerhans cell seem to be the precursor cells for LCH [2]. Clinical presentation of patients with LCH may vary in site and extent of involvement. In 45% of patients LCH manifests as a multisystem disease including 77% bone, 39% skin, 19% lymph node, 16% liver, 13% spleen, 13% oral mucosa, 10% lung, and 6% CNS involvement [3].

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DR ELISABETH ROIDER (Orcid ID : 0000-0003-0817-1923)
PROFESSOR MARTIN SCHALLER (Orcid ID : 0000-0002-7930-1919)
PROFESSOR REINHARD DUMMER (Orcid ID : 0000-0003-3962-7575)

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Individualized Treatment Approaches for Langerhans Cell Histiocytosis

E. Roider[1], C. Signer[3], B. Fehrenbacher[5], G. Metzler[4], M. Schaller[4], J. Kamarachev[1], K. Kerl[1], S. Balabanov[2], W. Jochum[4], W. Hoetzenecker[6], A. Cozzio[3], L.E. French[1], R. Dummer[1], E. Guenova[1,3,5]

AUTHOR AFFILIATIONS

[1]Department of Dermatology and [2]Department of Hematology and Oncology, University Hospital Zürich, University of Zurich, Zurich, Switzerland

[3]Department of Dermatology Venerology, Allergology, and [4]Institute of Pathology, Kantonsspital St. Gallen, St. Gallen, Switzerland

[5]Department of Dermatology, University Hospital Tübingen, Tübingen, Germany

[6]Department of Dermatology, Kepler University Hospital, Linz, Austria

CORRESPONDING AUTHOR

Emmanuella Guenova, M.D., Ph.D.

Department of Dermatology

University Hospital Zürich, Switzerland

Email: Emmanuella.Guenova@usz.ch

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DEAR EDITOR, Langerhans cell histiocytosis (LCH) belongs to the rare histiocytic disorders, and has an estimated incidence of 1-2 cases per million adults [1]. Myeloid dendritic cells that express the same antigens (CD1a, CD207) as epidermal Langerhans cell seem to be

the precursor cells for LCH [2]. Clinical presentation of patients with LCH may vary in site and extent of involvement. In 45% of patients LCH manifests as a multisystem disease including 77% bone, 39% skin, 19% lymph node, 16% liver, 13% spleen, 13% oral mucosa, 10% lung, and 6% CNS involvement [3]. Cutaneous manifestations usually present as purplish papules and an eczematiform skin eruption, commonly presenting as intertrigo. Other skin lesions may be petechial, vesicular, pustular, purpuric, or papulo-nodular [4]. Clinical appearance and pathology of LCH patients varies, emphasizing the need for an individualized treatment approach, as described in the three cases reported below.

Patient 1

We diagnosed a 59-year-old male patient with maculopapular lesions on the trunk and osteolytic bone lesions (fig. 1A). BRAFV600E was negative and a MAP2K1 deletion in exon 3 has been detected. Skin displayed perianal and oral ulcerations and a maculopapular eruption on the trunk. A skin biopsy displayed a strong positivity for CD1a, S100 and CD207 (fig. 1D). A bone marrow biopsy was negative and PET-CT imaging displayed lytic lesions of the spine, ribs, femur and os coxae. Initial treatment with 12 cycles of cytarabine chemotherapy (150 mg/m^2, day 1-5, every 29 days) resulted in a partial improvement at first. After 12 cycles the patient relapsed and treatment was changed to the MEK-inhibitor cobimetinib (60mg, day 1-21, every 29 days). Due to an increase in creatin kinase and myoglobulin, as well as rosacea-like facial eruptions, after 4 cycles dosage was reduced to 20mg resulting in an ongoing significant improvement of his cutaneous and extracutaneous lesions as displayed by PET-CT imaging (fig. 1F).

Patient 2

A 26 year-old female patient presented with multiple papulo-pustular lesions and erosions of the scalp, gingiva, genital and axillary region, and nearly intolerable pruritus (fig. 1B). Histological examination of the skin lesions revealed Birbeck granules (fig. 1E), as well as abundant large, oval, CD1a positive, CD68 negative cells with distinctive nuclei. We diagnosed the patient with BRAFV600E wild type skin limited LCH. Surgical excision of skin lesions and systemic administration of dimethyl fumarate remained ineffective. An off-label treatment with 50mg thalidomide daily, followed by a short-term and low dose treatment with systemic corticosteroids (25mg prednisone equivalent), as well as antihistamine and topical steroid treatment resulted in significant improvement in the patient's general and cutaneous condition.

Patient 3

An 84 year-old female patient presented with progressive pruritic maculopapular skin lesions on the trunk, intertriginous and gluteal region (fig. 1C). Histology and PCR showed a BRAFV600E (c.1799T>A) missense mutation in exon 15 and a strong positivity for CD1A, CD4, CD11c, Langerin, and S-100 protein. No systemic involvement was shown. Because itch was the major clinical problem, a symptomatic treatment with UVB 311nm and dapsone up to 100mg daily was administered. No clinical effect was shown after 8 weeks, and treatment replaced by systemic antihistamines. We discussed the possibility of a BRAF inhibitor treatment, but due to the good quality of life and lack of subjective symptoms a watchful waiting strategy was chosen.

LCH is an extremely heterogeneous disease, explaining the variety of published treatment. For skin-limited LCH, treatment with oral methotrexate, 6-mercaptopurine, topical corticosteroids, topical nitrogen mustard or oral thalidomide have been reported. In case of systemic involvement, vinblastine plus prednisone or the combination of vindesine, prednisone, cyclophosphamide, and etoposide reported event-free survival rates of 20 to 40 percent. Other treatment approaches include MACOP-B chemotherapy, the tyrosine kinase inhibitor imatinib, as well as curettage, surgery and radiotherapy. [5]. As recently reported, 65% percent of LCH patients bear the BRAF(V600E) mutation [6]. Multiple studies have described the deleterious effect of BRAF(V600E) mutations in LCH patients, highlighting its lower response to vinblastine plus a steroid as first-line chemotherapy, with increased relapse rates [7]. Even though BRAF inhibitors induce significant responses nearly all of these patients will relapse upon discontinuation of therapy. In adult patients an overall mortality of 3% has been reported. Nevertheless, long-term problems occur in about a third of all adult patients with multisystem involvement [8]. In summary, the above-described case series highlights the need for individualized treatment approaches, as well as joint multicenter efforts in order to investigate currently available treatment options.

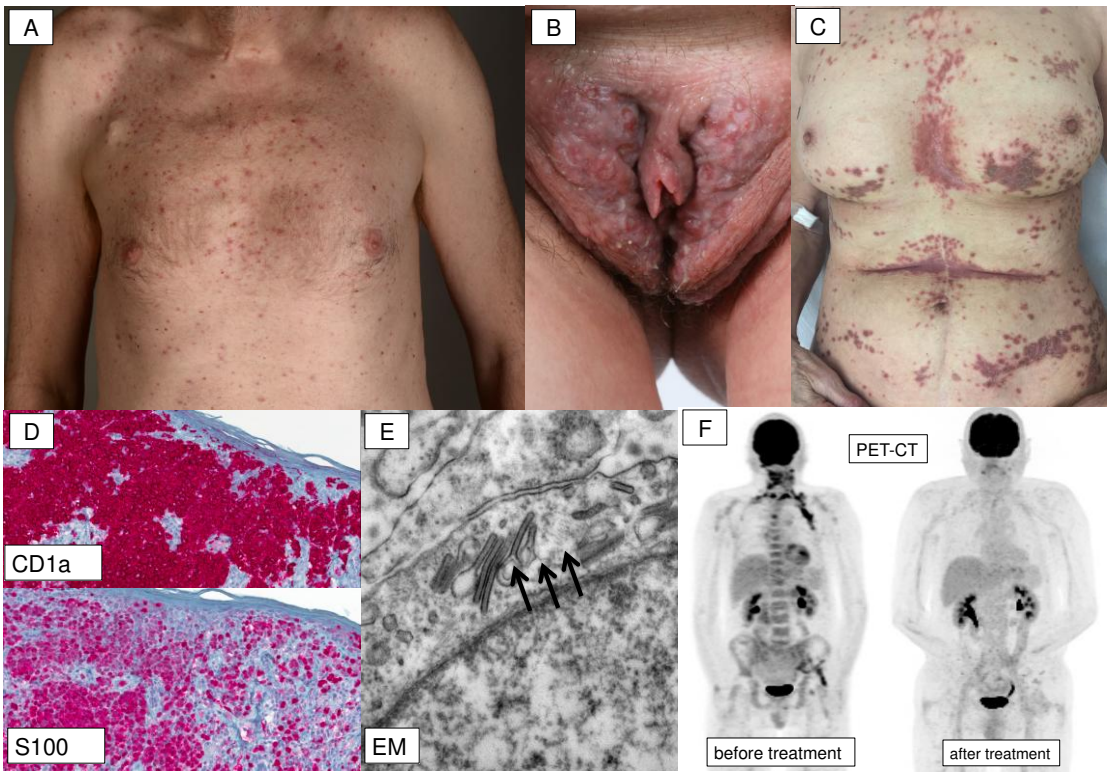

FIGURE 1. Clinical images of patient 1 (A), patient 2 (B), and patient 3 (C). Histology staining for CD1a, S100 (D) and electron microscopy images (E). PET-CT scan before and after treatment (F).

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